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Chemoradiotherapy Interactions in the Central Nervous System

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INTRODUCTION

With the advent of therapy for central nervous system (CNS) leukemia, a series of reports followed that described neurologic deterioration after combined treatment of either cranial radiotherapy (CrRT) and intrathecal methotrexate (IT MTX) or CrRT and IT cytosine arabinoside (cytarabine). Several weeks or months after receiving CrRT and concurrent IT chemotherapy for overt CNS leukemia, the reported patients developed progressive encephalopathy. Imaging studies revealed nonenhancing, periventricular hypodensity, especially along the lateral ventricles. Fatal cases revealed demyelination, with axonal swelling and fragmentation and with coagulative necrosis of the periventricular, central white matter. In the initial series of reports, this pattern had not been observed with either radiotherapy (RT) alone or IT chemotherapy alone. Thus, the prototypical chemoradiotherapy interaction in the CNS is necrotizing leukoencephalopathy (LEP) caused by CrRT and IT MTX [1]. An example of a patient who sustained this complication of therapy to prevent overt CNS leukemia is shown in Figure 1.

When systemic MTX therapy was intensified a few years later, such that some patients received intravenous MTX in addition to CrRT and IT MTX, the neurotoxicity rate was observed to increase. In one randomized trial, 9 of the first 20 patients on the CrRT, IT MTX, and intravenous MTX regimen developed LEP, requiring early closure of this treatment arm [2]. A review of all published cases indicated that the incidence of LEP in the combined treatment groups was greater than that predicted by the toxicity rates within the component subgroups (Fig. 2). Thus, the concept of interactions was proposed in which one treatment made the other more toxic, such that the combined effect was greater than the sum of the individual treatments. Thus, it was logical to conclude that combinations of therapeutic modalities should be avoided, especially RT. Although this has been largely successful for the prevention of overt CNS leukemia, attempts to prevent other CNS metastatic disease, established CNS leukemia, and primary brain tumors has led to a reduced efficacy of therapy, such that combination therapy generally remains the treatment of choice for most malignant neoplasms within the CNS [3–5].

Of course, there may be interactions between individual chemotherapeutic agents, such as the inhibition of MTX uptake of leukemia cells by hydrocortisone when IT MTX, cytarabine, and hydrocortisone are combined in IT ''triple therapy,'' but these chemotherapy-chemotherapy interactions are beyond the scope of this review on chemoradiotherapy interactions, nor will this compilation include RT-RT interactions or self-potentiation of self antagonism by either chemotherapy or RT alone. Instead, this article will focus on chemotherapy-RT interactions. The last dedicated review on this topic was published in 1980 [6].

CLASSIFICATION OF INTERACTIONS

Interactions of chemotherapy and RT in the CNS may be classified according to mechanism, net effect, clinical significance, reversibility, and timing relative to administration of therapy.

Synergism Versus Antagonism

The mechanism may be synergistic or antagonistic, resulting in a combined effect that is either greater than or less than expected based on the component therapies themselves. For synergism, the net effect must be more than additive or cumulative of the component effects. The prototypic example of synergism is the MTX-RT interaction in the CNS described above. Cisplatin and RT is another example both in terms of normal tissue effects, such as hearing loss, and therapeutically when both modalities are directed toward a malignant tumor within the CNS. Therapeutic antagonism may occur when preradiation chemotherapy results in hypoxia within the malignancy such that radiotherapy is less effective in the hypoxic areas.

Directionality

The interaction may be unidirectional or bidirectional (Table I). The former may be in either direction ($\rightarrow$ or $\leftarrow$), but the interaction occurs in one direction only. The latter occurs when the individual components affect one another ($\leftrightarrow$) either simultaneously or sequentially, with one direction occurring before the other. Unidirectional interactions are more common, such as chemotherapy

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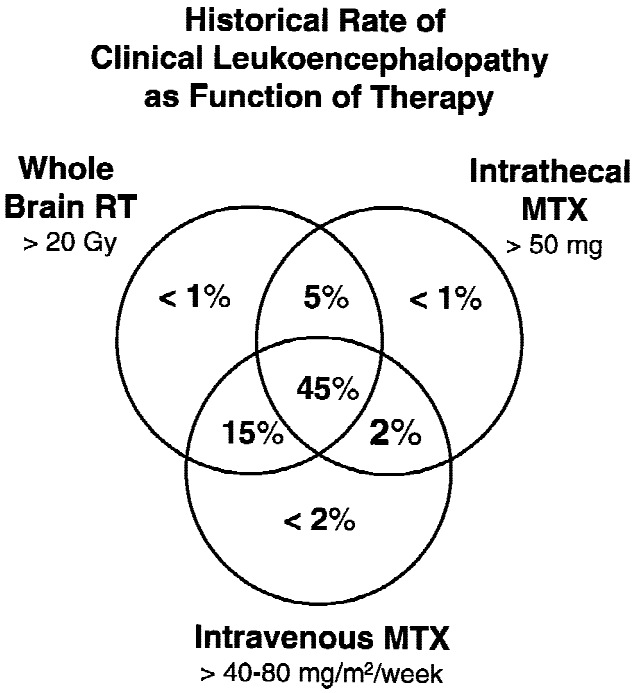

Fig. 1. Approximate rate of clinical leucoencephalopathy as a function of three treatment modalities, as determined from reports in the literature [1]. MTX, methotrexate; RT, radiotherapy.

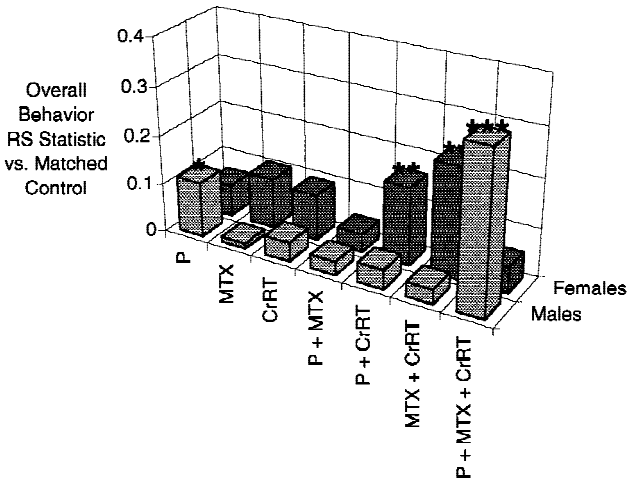

Fig. 2. The overall effects of one-, two- and three-agent combinations on behavior in 6-week-old rats that were treated at 17–18 days of age, as follows: predisolone (P), 18 mg/kg peritoneally on both day 17 and 18; methotrexate (MTX), 2 mg/kg peritoneally on day 18 only; CrRT, 10 Gy 1–3 hours after MTX (on day 18). Each bar represents a composite of 100 behavioral measures per experiment. One, two, and three asterisks designate $P < 0.01$, $P < 0.001$, and $P < 0.0001$, respectively, relative to match control with sham radiotherapy (RT) and no other therapy [12]. CrRT, cranial radiotherapy.

affecting the effectiveness or destructiveness of RT, or vice versa. An in vivo model of RT-induced spinal cord toxicity suggests that cytarabine, a widely used IT agent for eradication of CNS leukemia, is a potent radiosensitizer of normal neural tissue [7]. In this model, cytarabine is 1.4 times more potent than MTX as a radiosensitizer of the spinal cord. At least two patients who became blind after IT cytarabine and RT encompassing the optic chiasm have been reported [8]. Misonidazole, metronidazole, and bromodeoxyuridine are known radiosensitizers of gliomas. Misonidazole and metronidazole were tested extensively against human brain tumors without consistent success, however, to justify general application. Bromodeoxyuridine and buthionine sulfoximide are currently being evaluated for their efficacy as radiopotentiators of neoplastic neural tumors.

Another example of unidirectional interaction in the chemotherapy →RT direction is the ''recall'' of toxic effects of prior RT by chemotherapeutic agents, such as dactinomycin (Table I). The unusual feature here is that the chemotherapeutic agent may induce this interaction days, months, and even years *after* the RT has been administered. With prior spinal RT, dactinomycin may recall RT neurotoxicity and produce paraparesis [9], whereas dactinomycin alone has not been reported to cause spinal cord toxicity.

Radioprotection of normal CNS tissue by chemotherapy is a potentially beneficial interaction (Table I), but there has been only one recognized possibility with chemotherapy used in human cancer treatment. In one rodent model [10], pre-RT MTX decreased the frequency of paraparesis following spinal cord RT [11]. In another model, pre-RT MTX prevented RT-induced behavioral abnormalities, but this radioprotective effect was demonstrable only in male rats (Table II) [12]. In children with leukemia, IT MTX administered for 2–4 weeks prior to CrRT has been associated with improved IQ outcome compared with CrRT without prior IT MTX [13]. IT amifostine (WR-2721) is the most potent spinal cord radioprotector studied to date [14–16], and amifostine has the additional advantage of lacking radioprotection (and chemoprotection) of cancer in general, including CNS malignancies [17]. The rationale for a Phase I trial of IT amifostine for CrRT is discussed further below.

In the RT→ chemotherapy direction, RT-induced permeability may allow increased CNS entry of systemically administered drugs. In a rodent model, for example, CrRT permits increased entry of MTX after peritoneal injection [18]. A clinical example of this phenomenon has not been documented, however. On the contrary, cerebrospinal fluid (CSF) MTX after CrRT in humans at the doses of RT used has been demonstrated to be similar in radiated and nonirradiated patients. Other factors, such as the presence of overt CNS leukemia, have a much greater effect than prior RT on CNS levels of MTX after systemic administration [19]. An important consideration in exploiting potential RT→ chemotherapy interactions is the selectivity, or lack thereof, of RT-induced vascular

TABLE I. Chemoradiotherapy Interactions in the Central Nervous System: Mechanism of Interaction and Outcome*

	Terminology (examples)	
	Synergism	Antagonism
RT ← CT (CT affects RT)	Radiopotentiation Cytarabine, cisplatin, misonidazole, buthionine, sulfoximide, bromodeoxyuridine Radiation recall Cytarabine, dactinomycin	Radioprotection Amifostine, pre-RT MTX
RT → CT (RT affects CT)	Chemopotentiation Chemosensitization RT-induced MTX permeability of blood-brain barrier	Chemoprotection RT attenuation of IT, MTX-induced arachnoiditis
RT ↔ CT (RT and CT affect each other)	Mutual potentiation RT → cytarabine → recall? ←Mixed effects →	Mutual protection ? ← Mixed effects →

*RT, radiotherapy; CT, chemotherapy; MTX, methotrexate; IT MTX, intrathecal methotrexate.

TABLE II. Preradiotherapy Methotrexate Prevention of Radiotherapy-Induced Decrements in Behavior in 4-Week-Old Male Rats That Were Treated at 18 Days of Age With Methotrexate (2 mg/kg, intraperitoneally) 1–3 Hours Before Cranial Radiotherapy (10 Gy) and Weaned From the Mother at 21 Days of Age†

	Behavior score (mean ± SEM)			
Behavior	Control	RT	MTX	MTX + RT
Sit	44 ± 6	32 ± 3*	50 ± 4	43 ± 4
Attention	30 ± 4	19 ± 1*	31 ± 4	31 ± 3
Explore	25 ± 5	16 ± 2*	28 ± 4	22 ± 2

†Data from Mullenix et al. [12]. SEM, standard error of the mean; RT, radiotherapy; MTX, methotrexate.
*$P < 0.05$.

changes on normal brain capillaries versus those in brain tumors or CNS metastases. Because brain tumors generally enhance with intravenous contrast, and normal brain tissue does not, implying that brain tumors are already more permeable than normal neural tissue, it is likely that RT-induced changes in the capillary permeability will increase penetration of normal CNS tissue and cause undesirable neurotoxic reactions rather than enhance antitumor efficacy of systemically administered antineoplastic agents or irradiated brain tumors. Chemoprotection by RT is an unlikely concept, although successful RT of a brain tumor may diminish the need for adjuvant chemotherapy and thereby indirectly reduce drug-related toxicities. A specific example of how RT may reduce chemotherapy toxicity is the reported reduction in IT MTX-induced arachnoiditis in patients treated concurrently with CrRT [20]. The biologic basis for this interaction has been attributed to inhibition by ionizing radiation of the acute inflammatory response to IT MTX [19]. Other explanations are that RT alters the distribution of MTX in the CNS, such that the meninges are exposed to less MTX; RT increases the CNS concentrations of MTX antagonists, such as 5-methyltetrahydrofolate or thymidine; or RT synchronizes the cell cycle of susceptible populations of cells with the CNS away from the MTX-susceptible S-phase.

Bidirectional RT↔ chemotherapy interaction, in which each modality affects the other, is difficult to illustrate. One possibility is the combination of CrRT and cytarabine. CrRT may permit more cytarabine to enter the CNS after systemic administration as a result of increased capillary permeability, and a greater cytarabine neurotoxic reaction may occur. In turn, the increased distribution of the radiosensitizer within the CNS parenchyma may lead to intensified post-RT radiation recall by the chemotherapy agent.

Anatomic Site

The anatomic site of a chemoradiotherapeutic interaction depends primarily on the RT volume and dose and, to a lesser extent, on the neurotropism of the chemotherapy agent. The latter is exemplified by cerebellar toxicity of high-dose, intravenous cytarabine, the ototoxicity of cisplatin, and the periventricular necrosis of MTX, each of which is more likely with CrRT.

Beneficial Versus Deleterious

The outcome of a chemoradiotherapy interaction, whether it is beneficial or deleterious, is dependent on the combination and permutation of the interacting variables (Table III). An example of a beneficial interaction is the use of a radiation sensitizer, such as misonidazole or another ''antihypoxia agent'' to enhance RT-induced cell kill within a neoplasm. Another example of a beneficial interaction is the antagonism of MTX and CrRT in young male rats on a specific behavior (turning in response to a smell) [12]. There are many more examples of deleterious interactions than of beneficial interactions. A typical example is unexpected deafness that resulted from cisplatin therapy in a patient who was treated previously with CrRT [21].

TABLE III. Site of Interaction and Effect With Example of a Combined Beneficial Interaction

	Normal tissue	Tumor
Cytoprotection	Beneficial Amifostine (CT → RT)[a]	Deleterious!
Cytopotentiation	Deleterious!	Beneficial Misonidazole (CT → RT)

[a]CT, chemotherapy; RT, radiotherapy.

In considering possible permutations of RT and chemotherapy, it is theoretically possible to combine a favorable cytoprotective combination on normal tissue with a beneficial cytopotentiating combination on malignant cells. Such an approach has been suggested for treatment of neuroblastoma [22] successfully in the laboratory, albeit not within the CNS: potentiating RT on a malignant cells with misonidazole before RT and simultaneously decreasing the adverse RT toxicity on normal tissue surrounding the tumor by administering amifostine before RT (Table II).

Temporal Relationships of Therapy and Toxicities

Chemoradiotherapy interactions in the CNS may also be classified by temporal factors and severity [23]. The interaction may result in an acute, subacute, delayed, or chronic consequence. Within 24 hours, the combination of the first fraction of RT and a single dose of IT chemotherapy may cause acute neurologic deterioration, especially in patients with a large burden of neoplastic cells within the CNS that are sensitive to therapy [24]. Such a reaction may be the CNS equivalent of the tumor-lysis syndrome. Limiting the initial therapy to one or the other modality rather than combining them on the first day helps avoid the adverse acute effect. This acute interaction may not be due to the presence of active CNS leukemia, however, in that it has been observed after initiation of prophylactic CNS therapy in the absence of overt leukemia [25]. Subacute changes, such as somnolence syndrome and L'Hermitte spinal cord syndrome, may occur several days to a few weeks after initiating RT. Somnolence syndrome may also be an example of a chemoradiotherapy interaction, in that it is rare with CrRT alone with doses in the 18–30 Gy range, yet it is not uncommon in combination with IT chemotherapy with a dose of 24 Gy. Delayed or chronic toxicities occur months to years after the RT component of therapy and are represented prototypically by necrotizing leukoencephalopathy after CrRT and MTX therapy, as described above. In general, the acute and subacute reactions are transient, and the delayed-chronic sequelae are irreversible [23].

Severity

Interactions may also be classified by severity, ranging from clinically insignificant to life-threatening or fatal. Clinically-significant sequelae are generally obvious, although neuropsychometric testing may be necessary to discern underlying pathology, especially in the patient with compensated dysfunction. The latter is particularly evident in children who adjust to learning disabilities resulting from chemoradiotherapy of the CNS with alternate, compensatory mechanisms. Subclinical manifestations of RT-chemotherapy interactions are found frequently on magnetic resonance imaging (MRI) of the brain in patients treated with combined RT and IT chemotherapy. Nonenhancing, periventricular hypodensity is the most frequent abnormality, but most of these changes are not associated with detectable neurologic dysfunction and are frequently over-interpreted with respect to clinical significance [26]. The changes imaged by high-resolution techniques may be dramatic in appearance but are clinically insignificant and usually transient. Even computed tomography (CT) scans, which are less sensitive to these manifestations, will frequently demonstrate obvious changes that are completely reversible [27]. A not infrequent finding on CT scan is ''mineralizing microangiopathy,'' which appears as punctate calcification along the gray-white junction in the cerebral hemispheres. This abnormality is thought to be more a manifestation of the RT than the IT chemotherapy, but it is rarely observed with CrRT alone [1].

MEASUREMENT, QUANTITATION, AND DOSE DEPENDENCE

One of the best models for measurement of the behavioral effects of chemoradiotherapy interactions in the CNS is that of Mullenix and her coinvestigators [28]. Video cameras and computer programs are used to record and analyze spontaneous behaviors in rats at 6 weeks and 4 months of age after chemoradiotherapy at 17–18 days of age. The behaviors identified by the computer consist of five major body positions (stand, sit, rear, walk, and lay down) and eight modifiers (groom, head turn, look,

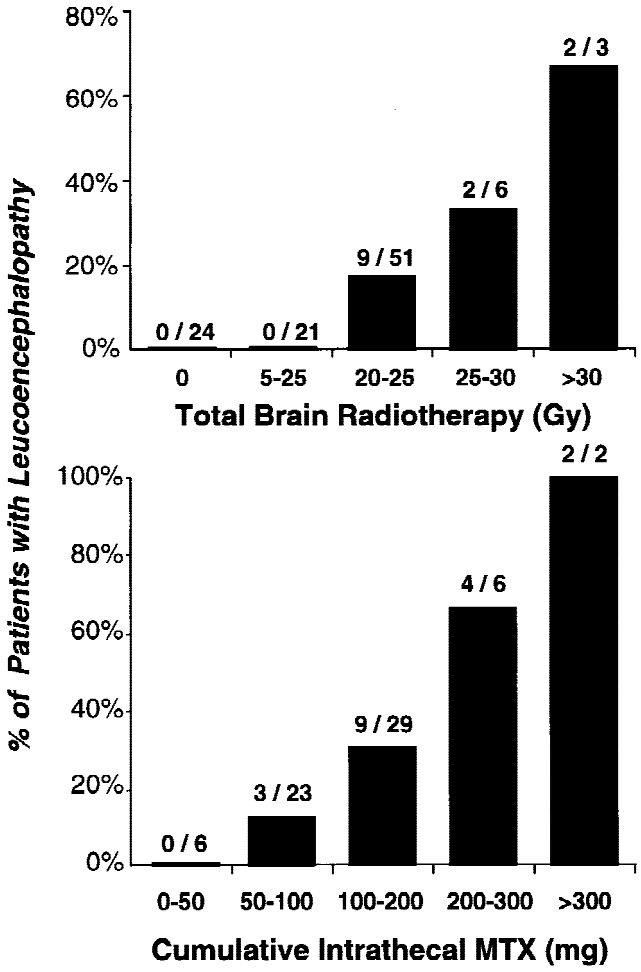

Fig. 3. Proportion of autopsies in children with leukemia demonstrating leucoencephalopathy [35]. MTX, methotrexate.

smell, sniff, turn, wash face, and blank or no recognized activity). An overall statistic derived from 100 behavioral measures of three distinctly different types can be computed for each experiment. An example of how chemoradiotherapy interactions can be quantitated by using this technique is shown in Figure 2.

Clearly, chemoradiotherapy interaction depends on the doses of the components. For most, if not all, agents, there is a threshold dose below which the interaction does not occur [1]. In an autopsy series of children with leukemia, there was no evidence for leukoencephalopathy when the lifetime dose of CrRT was below 500 cGy and the cumulative dose of intrathecal MTX was below 50 mg (Fig. 3) [1]. Above the threshold, the dose dependence may be continuous or discontinuous, linear or nonlinear, additive or multiplicative, synergistic or antagonistic. In a rat model, behaviors 1–3 months after CrRT, intraperitoneal MTX, and intraperitoneal prednisolone were affected either adversely or beneficially by increased doses of the chemotherapy agent [12]. Doubling the dose of MTX, for example, significantly reversed the

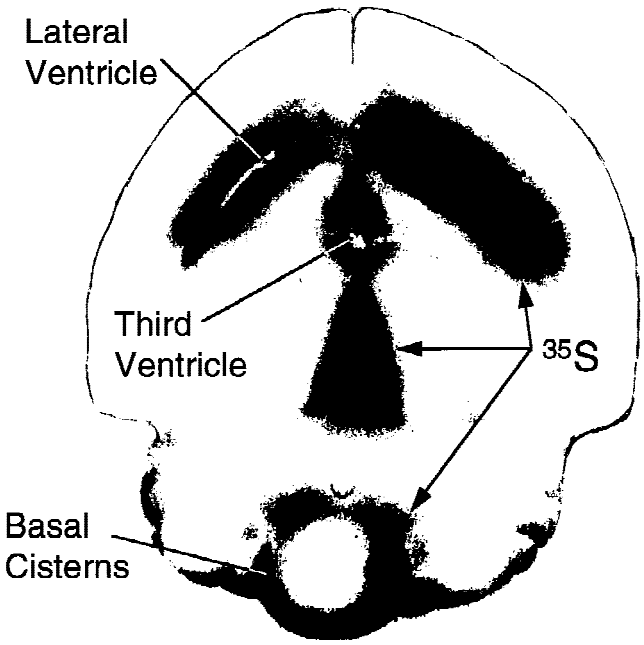

Fig. 4. Intracerebral distribution of ^{35}S-amifostine 45 minutes after lateral ventricle injection in the adult rat [15].

antagonism of MTX and CrRT in male rats, such that the animals were more instead of less able to turn rapidly toward a smell [12].

OTHER VARIABLES

The nature or severity of a chemoradiotherapy interaction in the CNS may depend on other variables. Age is a strong variable, with the developing CNS in general at more risk to manifest interactions than the CNS in a mature host. Gender is another variable that is becoming increasingly appreciated. Girls are more vulnerable to the deleterious effects of CrRT [29,30], but boys appear to be more vulnerable to the adverse interaction of CrRT and IT MTX [30]. On the other hand, the radioprotective effect of pre-RT MTX described above in a rat model was apparent in males and not females [12]. The combination of CrRT and systemically administered MTX appears to be more neurotoxic to females than males both in humans [29] and in rats (Fig. 2) [12]. Another striking example of a sex difference is a behavior-specific synergism between MTX and CrRT that results in a delayed response to smell in the female and a more rapid response in the male [12].

INTERACTIONS IN THE DEVELOPING CNS

Intra-CSF administration should be considered for CNS protection, because laboratory studies have shown significant neuroprotection when amifostine was delivered by this route of administration. In adult rats, dose-

modifying factors for limb paralysis after spinal radiotherapy of 1.3–1.6 were observed with intraventricular amifostine [14,16]. These protection factors are among the highest recorded for CNS protection, and there is reason to believe that they would be even higher for brain irradiation in the developing CNS [31–34]. For radiotherapy, intrathecal chemotherapy, and systemically administered chemotherapy, the most vulnerable structure in the developing brain is the subependymal zone [31,33]. The excellent distribution of amifostine and WR-1065 into this zone after intraventricular administration (Fig. 4) indicates that intraventricular amifostine is likely to be an effective cytoprotector of the developing CNS [31,33].

Before a Phase I trial of intrathecal amifostine is undertaken, the pharmacokinetics and clinical toxicities of the agent delivered by this route of administration should be determined in a large animal model. Ultimately, intrathecal amifostine should be tested for radioprotection in children with brain tumors or CNS leukemia and as a chemoprotector for intrathecal alkylating agents, like thiotepa, mafosfamide, and 4-hydroperoxycyclophosphamide. It may also be useful against intrathecal methotrexate and cytosine arabinoside, the most frequently administered intrathecal agents, and against systemic chemotherapies with CNS toxicities.

ROLE OF INTERACTIONS IN CNS TOXICITY

At least three major factors predict that chemoradiotherapy interactions in the CNS are increasing: 1) the increasing use of multimodal, combination therapies in cancer medicine; 2) the increasing incidence of CNS metastases and primary brain tumors; and 3) the more aggressive approach being taken to improve cancer treatment results, including the high-dose approach facilitated by hematopoietic stem cell rescue and a variety of increased dose-intensity applications. It is reasonable to assume that far more interactions are occurring in the human CNS than have been identified or even speculated upon in this review. This review attempts to provide a framework of classification that can help organize future investigations into chemoradiotherapy interactions. The problem is complex, as is the basic biology and circuitry of the CNS itself, but an organized approach should facilitate solutions.

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